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DOES TRAMADOL ABUSE WORSEN COMPLICATIONS AMONG URAEMICS?

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ABSTRACT

Tramadol abuse is widely increasing phenomena especially among young adults. In this study, we studied the prevalence of tramadol abuse among uremics (< 40 years old) on hemodailysis replacement therapy then we evaluated its effect on common uremia and hemodilaysis complications; anemia, hypertension and occurrence cramps during sessions. Tramadol abusers had shown significantly lower levels of hemoglobin, hematocrit and reticulocytes production index relative to uremics nonabusers. In addition, uremics on tramadol had showed higher incidence of systolic and diastolic hypertension. Moreover, higher incidence of cramps on hemodialysis sessions was shown in tramadol abusers.

Keywords: Tramadol, Terminal clinical manifestation, Hyperparathyroidism.

INTRODUCTION

In Egypt, tramadol abuse is an increasingly alarming phenomenon, which becomes highly demonstrated in the recent years. Popularity of tramadol is due to its cheap prices, wide availability and also false allegations, especially among youth and middle aged groups, that tarmadol can improve the premature ejaculatory function and cause extended orgasm and increase sexual [1].

Uremia can be defined as the terminal clinical manifestation of kidney failure (also called renal failure) [2]. It is associated with inadequate excretory, regulatory and endocrine function of the kidneys [3]. Uremia is characterized with group of clinical and laboratory clinical manifestations involving the different body systems.

Anemia is a common finding among uremic patients. It is always normocytic and normochromic with reduced reticulocytic count [4]. Bone marrow hypofunction among uremic is mainly due to decreased erythropiotin hormone production. In addition, other factors also have roles as decreased iron and folic acid, hyperparathyroidism, aluminum toxicity and mild hemolysis with bleeding (mostly gastrointestinal) [5].

Hypertension is also a common manifestation among uremics. About 50-90% of uremic patients are hypertensive with blood pressure >140/90 mmHg. While prevalence of hypertensive in sex and age matched nonuraemic sis about 25% [6]. *Foley et al. (1996*) reported that the risk for congestive heart failure increased 40 % with every 10 mmHg increase in systolic blood pressure.

Muscle cramps are a common complication in patients receiving dialysis. Muscle cramps can involve the legs, most commonly in the feet, but can also involve arms and hands, as well as abdominal muscles. It is estimated that 33% to 86% of patients receiving dialysis have experienced cramps. In a study from 2001, 25% of hemodialysis patients reported two or more cramps weekly.

In this work we have studied tramadol abuse in

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middle aged uremics on hemodialysis in a multicenters study in 3 centers for hemodilaysis in Dakahlyia governate. Effect of tramadol on severity of anemia, hypertension and incidence of muscle cramps was evaluated by comparison between tramadol abusers and matched group of uremics tramadol nonabusers.

PATIENTS AND METHODS

The study was conducted in 3 hospitals (Sherbeen general hospital, Mansoura general hospital and Mansoura university hospitals) on uremics aged <40 years on hemodilaysis.

Study population

The study was designed and conducted after approval from Mansoura Faculty of Medicine research ethical committee. Signed informed consents were taken from all persons involved in the study as controls or substance abusers. Confidentiality of data was respected.

The inclusion criteria in our study were uremics, aged blow 40 years, without history of recent blood transfusion within 3 months preceding the study and with negative screen for other drugs of abuse. Seventy-four uremic patients attending to the hemodilaysis units of the 3 hospitals were involved in the study after fulfilling the inclusion criteria of the study. No stipend was provided, however participants were informed about the results of their laboratory tests.

For drug abuse screening, after having informed consent, 30 ml urine was obtained from each participant. Each sample was collected in a dry, labeled container. Samples were screened for 5 substances of abuse using Emit® d.a.u. TM (drug of abuse in urine) for opiate, cannabis, benzodiazepines, barbiturates and tramadol. After the initial screens, positive cases were confirmed by thin layer chromatography. For confirmed Tramadol positive cases, was measured by Gas chromatography (YOUNGLIN, 2000, KOREA). Standard curves were done from 100 to10,000 ng/mL to estimate plasma tramadol levels.

Complete blood counts (CBC) were done for all patients involved in our study. Red blood cells (RBCs) parameters (Hematocrite (Hct), RBCs counts and hemoglobin (Hbn) levels) were used to in our study. Mean corpuscular volume (MCV) was estimated from formula [MCV=(Hct/RBCs count)*10] . Its normal range: 80-100 fL [7]. While reticulocyte production index (RPI) was estimated from formula [RPI= reticulcytic count*Hct/normal Hct(45%)]. Then RPI results were corrected according to Hct values of each case. The reticulocyte index (RI) should be between 0.5% and 2.5% for a healthy individual [8]. Pre-session blood pressures were estimated from sheets of 12 hemodialysis sessions. History of muscle cramps was estimated within 12 sessions.

Statistical analysis

Statistical analyses were performed using PRISM 5 (Graph Pad Software Inc., San Diego, CA). Fisher exact test and Chi-sqaure tests were used to determine the significance of differences in presessional blood pressure and incidence of cramps during hemodialysis between tramadol abusers and non abusers uremic patients. Correlations between tramadol serum levels and the different parameters of the study were performed with the use of Pearson rank correlation coefficients. Comparisons between both groups regarding Hct, Hbn, RBCs count, MCV, RPI, SBP and DBP were performed with a paired Mann-whitney test.

RESULTS

Prevalence of tramadol abuse among middle aged uremics on hemodialysis

Seventy-two uremic patients (57 males 22 females) have satisfied the inclusion criteria of the study and gave signed consent for participation. Age of patients ranged between 19-39 years with a mean age 30.1±5 Yrs. According to our EMIT screen data, which were further confirmed by TLC study, the ureamic patients were divided in to tramadol abuser groups (34 cases) and non tramadol abusers (45 cases). Tramadol abuse showed more prevalence in males (44% of the studied male) in comparison to females (27.3% of the studied females). Tramadol abuse was more prevalent in urban (59% of studied tramadol abusers) than rural areas (only 41% of the studied abusers). The abusers showed tramadol serum levels ranging from 2-4.8 µg/ml with a mean tramadol level (3±0.5 µg/ml).

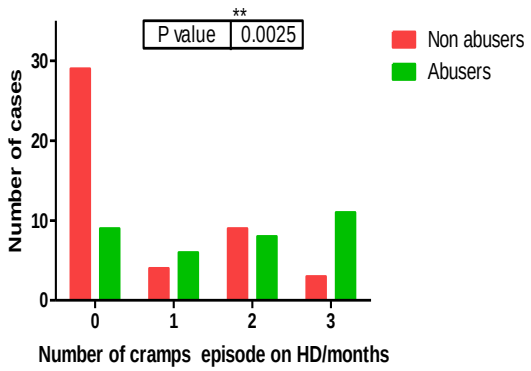
Table 1. Heamtocrite (Hct), red blood cells (RBCs) count, hemoglobin (Hbn), mean corpuscular volume (MCV), reticulcyte production index (RPI), systolic blood pressure (SBP) and diastolic blood pressure (DBP) among abusers and nonabusrs during HD sessions within one month

	Abusers	Nonabusers	P-value
Hct	7.8± 0.44	8.3±0.6	<0.0001*** (a)
RBC count	3.91E+12 ± 3.93E+11	4.045E+12 ± 4.163E+11	0.1599 (a)
Hbn	0.349412 ± 0.03	0.372632 ± 0.029009	0.0015** (a)
MCV	89.6± 6.1	92.55 ± 6.83	0.0652 (a)
RPI	1.4 ±0.35	1.65± 0.38	0.0148* (a)
SBP ≤140 mmHg	23	8	0.0195* (b)

>140mmHg	22	26	
SBP (M±SD)	157± 13	143.9±8.3	0.0006*** (a)
DBP ≤90 mmHg >90mmHg	 6 39	 16 18	 0.0019** (b)
DBP	97.1±8.3	102± 6.7 mmHg	0.0159* (a)

Means that p-value was estimated by Mann-whitney test, while (b) means that p-value was estimated by Fisher exact test

Fig 1. Incidence of cramps episodes among abusers and nonabusrs during HD sessions within one month



Effect of tramadol abuse on complications among studied uremic patients

In our study, hemoglobin in all studied cases, without blood transfucion 3 months preceding the study was ranging from 7- 9.5 g/dl. Mean corpuscular volume ranging from 80-100 F/L (normocytic anemia) and reticulocyte production index ranging from 0.8-2.6.

As shown in table (1). Our data revealed significant difference among tramadol abusers and non-abuers in Hemoglobin (p <0.0001), Hct (p= 0.0015) and RPI (p=0.0148). There was no significant difference between both groups regarding RBCs count (p=0.1599) nor MCV (p=0.0652).

Tramadol was shown to significantly increase both systolic and diastolic blood pressures among abusers with p-values (0.0006 and 0.0159 respectively).

Incidence of cramps within one month in hemodialysis sessions was found significantly higher among tramadol abusers as shown in figure (1).

We have found significant correlations between tramadol serum levels Hbn (r= -0.46 and p-value 0.0081; Pearson rank correlation). The correlation was not significant with the other RBCs parameters. Also there was no correlation between tramadol serum levels and blood pressure changes or incidence of cramps episodes during hemodialysis sessions.

DISCUSSION

To the best of our knowledge, this is the first time to investigate the effect of tramadol abuse on complications commonly found in middle age uremic patients on hemodilaysis replacement therapy. We have conducted a multicenter study considering prevalence of tramadol abuse among uremic patients receiving hemodilaysis and the effect of tramadol on commonly encountered clinical problems of these patients group. It was a surprise that we have found about 43% of the studied cases were positive to tramadol, but this may be due to the study was only targeting the uremics aged blow 40 years and it was reported that substance abuse is more prevalent among adults in early and middle age groups [9], so this high prevalence is expected. Furthermore, Our high prevalence may be due to the effect of uremia on psychological condition of this age group as they main feeling is that they have lost a good life quality and they are obligated to deal with long life therapy without futures hopes of recover except after renal transplant operations which are not available for most cases due to clinical, ethical of financial limitations. Also some of patients started tramadol as a potent analgesic to relieve their headaches, bone aches and muscle cramps then they were changed to abusers by time, while their first intention was to relieve the pain and alleviate suffering. Regarding gender, we have found tramadol positive samples were more prevalent in males than females (44% and 27.3% respectively). This was in accordance with other studies reported more prevalence of abuse, generally, among males as drugs are more available for males and substance abuse is more is more socially accepted among males [10, 11]. Also in our study, females are not easily motivated to share in a study considering drug abuse, but we think that this will not affect statistically the robustness of our data.

Also our data showed that tramadol abuse was more prevalent in urban areas in comparison to rural areas due to more social relationships and family atmosphere in rural areas, which is expected to alleviate the uremics psychological stress. In addition to more strict supervision on the family young aged adults, which may be a barrier against abuse in rural areas.

The current work results showed tramadol serum levels ranging from 2-4.8 µg/ml. *Winek et al. (2001)* had reported therapeutic tramadol level range about (0.1-0.6 µg/ml). This means that the studies cases showed high levels of tramadol, which is mostly due to their tolerance to tramadol. This tolerance is considered as criteria for abuse as the abusers are continuously in need to increased the dose to maintain the first pleasurable effect [12]. In parallel, this finding means that these patients had toxic tramadol serum levels.

Our data regarding Hbn and MCV are in accordance with the previous data as normocytic anemia is a common finding among uremic patients. RPI <2 in most cases indicating anemia due to a defect in RBCs production, which is mostly explained by defective erythropoietin among uremics as erythropoietin is normally produced by the endothelia of proximal tubules of the functioning kidneys [13]. We did not find previously published paper considering tramadol effect on RBCs, but some reports were published in eHealth Med website considering reduced RBCs number and bone marrow depression especially in old ages females depending on FDA reports and social media.

In our study, tramadol was shown to increase the blood pressure among abuser in comparison to the non-abuser group inspite being on antihypertensives therapy. Tramadol induced hypertension was previously explained as a feature of tramadol-induced serotonin syndrome due to the Serotonin-Norepinephrine Reuptake Inhibitor (SNRI) properties of the drug, which may include neuromuscular hyperactivity (myoclonus and hyperreflexia), autonomic hyperactivity (tachycardia, hypertension and pyrexia) and altered mental state (usually agitation, excitement and later confusion). Serotonin syndrome is more common in tramadol abusers taking in combination with other serotonergic medications such as antidepressants [14]. Which may be prescribed for middle ages uremics going under hemodialysis to control the associated depressive mood?

In our study, we have found that tramadol increased the incidence of muscle cramps among uremics during hemodialysis. The pathogenesis of muscle cramps during hemodialysis is unknown. However three predisposing factors were suggested, which are hypotension (unlikely reported among our abusers), dehydration to blow dry weight (by the end of the sessions) and hyponatremia. We are mainly suggesting hyponatemia to be the triggering factor of increased cramps among tramadol abusers. Opioids are known to affect renal excretion of water and sodium, through numerous mechanisms that result in antidiuresis. In addition, tramadol enhances release of serotonin to achieve its full analgesic effect, and selective serotonin reuptake inhibitors (venlafaxine) are known culprits in hyponatraemia by stimulating ADH release [15]. Therefore, both opioid and serotonin pathways may have acted in synergy to result in hyponatraemia, which can trigger cramps during the hemodialysis sessions.

Our findings in this study are important for several reasons. Firstly, we have found high prevalence for tramadol abuse among uremics on hemodialysis for different reasons. Mostly due at medical misuse as analgesic and also some abused tramadol as a recreational drug to alleviate the depressive mood cause by the end stage disease. This should attract our attention for the importance of supportive psychotherapy for uremic patients with more concern to the middle age group and also we should pay more attention to medical prescriptions including tramadol as an analgesic. Secondly, we have found that tramadol increased the incidence of anemia, hypertension and muscle cramps among our patient. Hence we should minimize its clinical use as analgesic among uremic patient, specially with its well known addictive potentials as abusers mostly will be tolerant to its effect and will attain by time very high serum levels which mostly exceeds the normal toxic level. This will leads to more negative drawbacks upon their general health conditions and quality of life. Thirdly, we recommend more limitations on tramadol prescription and more penalties to persons who facilitate its illegal marketing. We also recommend its availability in only large referral hospitals under strict supervision on its use.

CONCLUSION

We can conclude that tramadol abuse was found to be highly prevalent among the young uremics in our locality. We have found that tramadol worsened anemia among abusers. Furthermore, it worsened control of hypertension among abusers. Moreover, tramadol was shown to increase the incidence of cramps during the hemodialysis sessions among abusers. We recommend other studies to study tramado, abuse effect on other uremia and hemodailysis complications. Also other mechanistic studies are required to explain the fore mentioned findings.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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